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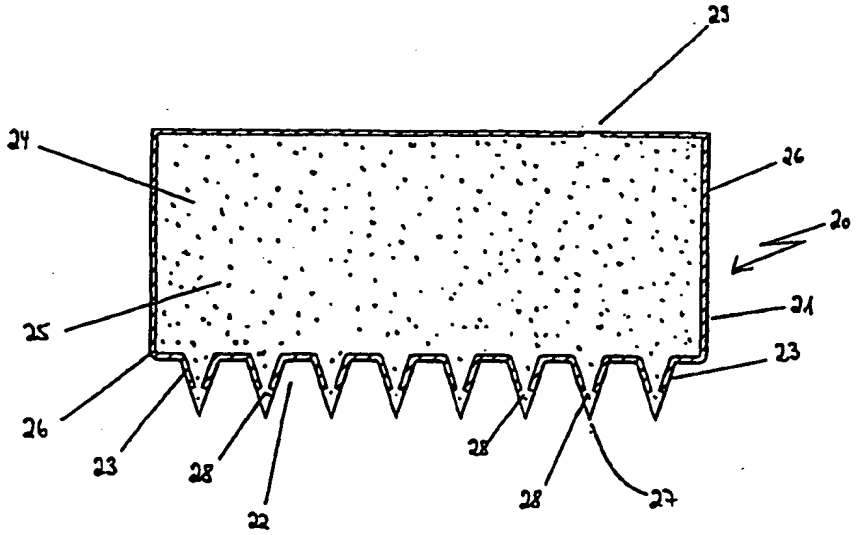

(57) Abstract

The invention concerns a novel transcorneal drug-release system.

(57) Zusammenfassung

Die vorliegende Erfindung betrifft ein neues transcorneales Arzneimittelfreigabesystem.

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TRANSCORNEAL DRUG-RELEASE SYSTEM

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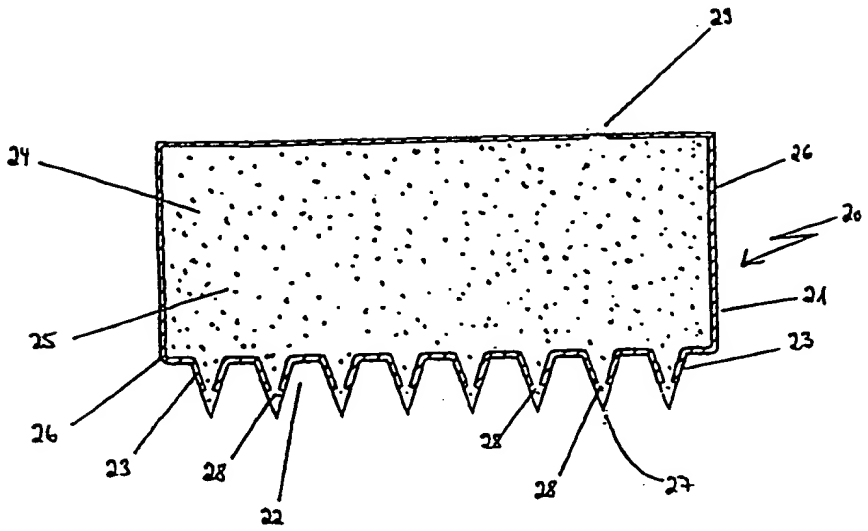
Abstract

The invention concerns a novel transcorneal drug-release system.



The present invention concerns a new drug-release system for controlled release of drugs over a longer period.

A transcorneal system for controlled supply of drugs is claimed according to the invention, bypassing the gastrointestinal tract, which essentially consists of a device that makes it possible to administer a drug over a longer period, bypassing the corneal skin layers.

The device according to the invention essentially consists of a reservoir for the drug and at least one, typically several, microspikes provided with capillary openings that are connected to the reservoir so that the drug reaches the microspikes in the form of an active ingredient-containing solution from the reservoir. When the transcorneal system is placed on the skin, the stratum corneum and optionally the epidermis are penetrated by the microspikes so that direct access is offered to the innervated skin layer. The drug can therefore reach the vascularized sections of the skin through the capillary openings of the microspikes to then be taken up in the circulation via the capillary circulation system. Instead of microspikes, microbezels can also be used, which then scarify the skin when the system is applied.

An essential advantage of the system according to the invention is that the skin barrier for transdermally administered drugs (the stratum corneum) is bypassed in the system according to the invention. It is precisely the individually different properties of the uppermost stratum corneum in patients that are the reason that problems like deficient bioavailability and allergies

occur during transdermal administration of active ingredients. A particular advantage of transcorneal administration is that this type of application is not restricted merely to active ingredients that penetrate through the skin, as is the case in transdermal administration. Appropriate active ingredients include analgesics, e.g., morphine, naltrexone, fentanyl, oxymorphone, anti-Parkinson agents like L-dopa, pramipexole; cardiocirculatory agents, nitroglycerin, agents against high blood pressure and vasodilatory diseases, like clonidine, nifidepine, verapamil, diltiazam; anticoagulants, like heparin, hirudin; agents for long-term therapy in cancer diseases and immune diseases; agents for long-term treatment and addiction therapy; peptides; ACE inhibitors; neurokinin antagonists; hormones, like estradiol.

The active ingredient is ordinarily present in the form of a solution in order to guarantee trouble-free transport through the capillary openings in the microspikes of the transcorneal system. In principle, all physiologically compatible solvents or solvent mixtures in which the active ingredient dissolves in sufficient amount can be used. Sufficient amount is understood to mean those concentrations of active ingredients in the solvent that make it possible to administer a therapeutically effective amount of active ingredient.

Preferred solvents are water and ethanol. Should it be necessary, solubilizers and sequestering agents can be used to increase the solubility of the active ingredient in the solvent. Sensitive active ingredients can be provided with additives to increase storage stability.

The system according to the invention contains a reservoir for storage of the active ingredient solution, in which a liquid-conducting connection between the reservoir and microspikes makes it possible for the drug to be conveyed from the reservoir to the capillary openings of the microspike to beneath the stratum corneum so that the drug can be introduced directly to the circulation, bypassing the outer skin layer.

Transport of the drug, for example, in the form of an aqueous solution, can occur, on the one hand, "passively," i.e., by the concentration gradient present between the concentration of active ingredient solution in the reservoir and in the blood, or "actively," for example, by an overpressure stored in the reservoir, electrostatic or capillary forces, or a pump integrated in the system. Active transport of the active ingredient solution is preferred, for example, by a pump or a piezoelectric membrane. The volume flow (mL/time) of the drugs can be set or controlled by one or more additional valves or a throttle zone between the reservoir and the microspikes.

Depending on the size of the reservoir, the active ingredient concentration and the required therapeutic dose, the transcorneal system according to the invention is suitable for an administration time of from several days to 4 weeks or longer, preferably 7-14 days.

In one embodiment the system is miniaturized with respect to its dimensions and weight so much that it can be worn without difficulty over a longer period on the skin or attached in the

skin, like a patch or wristwatch. Attachment of the transcorneal system can occur by means of an armband, a skin-compatible adhesive or also through the microspikes themselves.

Production of the system according to the invention, as well as filling the reservoir, occur under controlled conditions — for reasons of drug safety the system according to the invention can be packed or sealed airtight under sterile conditions up to use.

Ordinarily the reservoir and microspikes of the system according to the invention form a one-part or multipart structural unit in a housing. However, embodiments are conceivable in which the reservoir and microspikes are separated from each other by design and connected by a thin tube or capillary. This is particularly advantageous when larger amounts of drug are to be administered over a longer period.

The technical and design layout of the microspikes, as well as the capillary openings that serve for supply of the active ingredient solution, are of decisive significance for function of the transcorneal system according to the invention.

For penetration of the stratum corneum it is essential that the microspikes have a length of at least 10 μm, preferably 50-100 μm, especially up to 1 mm. The microspikes according to the invention are conical or cylindrical, in which the radii of curvature of the spike tips are typically in the μm range, preferably smaller than 10 μm. Damage to the skin and pain sensitivity during administration are kept as low as possible because of this. To ensure adequate supply of active ingredient solution into the capillary blood circulation of the patient, the microspikes according to the invention have capillary openings, for example in the form of holes or slits or a combination of both. Microspikes made of a material of defined porosity also permit supply of the active ingredient solution.

Particular embodiments of the microspikes according to the invention can have capillary openings in the form of a combination of a central hole with slits on the outside.

Transport of the active ingredient solution can be supported or regulated as a function of the viscosity of the solution by mechanical, electrical, chemical and/or surface active forces. For reasons of redundancy (but also to adjust the volume flow and conduction resistance) a number of microspikes are preferably used for the transcorneal system. The microspikes are ordinarily arranged on a surface that forms the side of the transcorneal system facing the skin. This surface can be between a few square millimeters and a few square centimeters. The typical number of microspikes lies between 10 and 100, this statement in no way limiting the idea of the invention.

The active ingredient from which the microspikes are produced must be skin-compatible and biocompatible. In the interest of cost-effective mass production, glasses and metals, e.g., titanium, are suitable, in addition to ceramic materials. Plastics that are easy to process are to be preferred. Biodegradable polymers, like polylactides and others, have the advantage that any material particles of the spikes remaining in the skin can be broken down. Biodegradable

polymers have long been known from the prior art and have proven themselves as suture material and bone splints.

Figure 1 shows a particularly simple configuration of the transcorneal system (20) in an axial section. The system consists of a container (21) with microspikes (23) formed on the bottom (22). The internal space of the container serves as reservoir (24) to accept the active ingredient solution (25). Depending on the viscosity, the active ingredient solution is present as such directly in the reservoir or is stored in a matrix, for example from an absorbent material or a polymer. The container and microspikes have a liquid-tight outer wall (26), which is mechanically stable so that the system can be placed on the skin for activation of drug release and the microspikes forced with light pressure into the skin. Since the outer wall (26) is penetrated in the region of tips (27) of the microspike and forms an outlet opening (28), the active ingredient solution because of capillary force can reach the capillary circulation system, bypassing the transcorneal skin layer, and from there exerts its systemic effect. A device is optionally provided in the region of the reservoir to create pressure equalization — vent (29). The vent is ordinarily provided with a filter so that contaminants cannot reach the system. To support volume flow of the active ingredient solution a device can be provided so that the reservoir can be additionally exposed to pressure. Filling of the system occurs, for example, by injection of the active ingredient solution into the reservoir, by immersion of the system in an active ingredient solution or by insertion of an active ingredient-impregnated matrix into the system. It goes without saying that in the last named case the transcorneal system is constructed in two parts, for example, from a lower part that forms the microspikes and an upper part with which the system is closed after insertion of the active ingredient matrix. Depending on the type of active ingredient, this can be present in an aqueous or organic physiologically compatible solvent or solvent mixture in dissolved form. Appropriate solvents include water, ethanol, propanol and their mixtures. However, the active ingredients can also be dissolved in a matrix consisting of a gel, for example, from polymer material.

Thermoplastics that can be sintered in a mold starting from a fine-grained granulate are primarily considered as material for production of the container and microspikes. By appropriate choice of the parameters pressure, temperature (typically below the melting point of the material) and time, a reproducible porosity (typically 50%) is set. By deliberate melting of the component surface, this is then closed so that a porous container with a tight outer wall is formed. Wall regions that are to be kept permeable, e.g., the vents, spike tips, are kept below the melting point by cooling. To seal the porous wall, coatings and sealings are also considered, but this requires higher manufacturing costs. The degree of porosity and the outlet cross section on the spike tips are variable within certain limits and so are the parameters for adjustment of the dosage rate. Other appropriate materials include polyethylene, polypropylene or polysulfone.

A further developed system is shown in Figure 2. Transcorneal system (30) consists of a housing bottom (31a) and a housing top (31b). The housing bottom (31a) contains microspikes (32) with capillary openings (33) on the side facing the skin surface, only three of which (but enlarged) are shown in the drawing for better depiction. The reservoir (34) for the active ingredient solution is formed by a moving piston (37) and by a bellows seal (38) on the sides of the housing bottom. The bellows seal can naturally be replaced by other means of sealing, for example, a precision-fit guide of the piston and the housing bottom. The housing top contains the micropump (39), which exerts a defined pressure on the piston and thus administers the active ingredient through the microspikes into the capillary circulation system. Microvalves (39a) can be arranged on the inside of the housing bottom in front of the capillary openings in order to prevent premature release of the drug. The pressure on the piston can occur pneumatically through the pump, but also in another embodiment can occur purely mechanically via a miniaturized electric motor and a linkage connected to it.

To improve the controllability and regulatability in the active ingredient dosage the system can be expanded by microsensors (39c), microactuators (39e), e.g., for active drive of the microvalves (not shown) and an electronic circuit (39b) with input-output capability (39d) and a power supply. The sensors primarily serve to detect and monitor controlled output and variables, like, e.g., the active ingredient concentration in the blood, the temperature or activity of the patient and to detect and monitor system quantities, like, e.g., time, flow rate, pressure, temperature. The storage region of the electronic circuit is programmable with reference data and parameters by the manufacturer or the doctor or patient by an appropriate interface. The measured values of the sensors are detected and processed by the electronics. The control signals for microactuators are derived according to the stipulated control and regulation functions. An essential component of the transcorneal system according to the invention is the configuration of the microspikes.

Embodiments of spikes (41) are shown in Figure 3. Figure 3a shows a spike (41), porous on the tip and thus kept permeable for the active ingredient solution. Figure 3b is a spike (42) with a completely tight outer wall. The tip has a continuation (44), which breaks off during insertion at its root, the predetermined rupture point (43), and thus opens the previously tight spike tip at the rupture site. Another possibility for opening of the spike tip consists of pulling off the initially closed spike tips with a sealing film (45) and thus "tearing off" the spike tips (Figure 3c). To anchor the transcorneal system, barbs can be formed on the spikes, see Figure 3d. The spikes are essentially made from a biologically compatible material, like metals, ceramics and polymers, for example, biodegradable polymers based on glycolides and/or lactides, possibly as copolymers with other biodegradable polymers. The spikes can also be made from a porous

material permeable to the active ingredient, for example, thermoplastic, so that the active ingredient is released over the entire surface of the spikes.

Figure 4 shows a trough-like reservoir (50) in which the active ingredient solution (51) is outwardly sealed with an elastic membrane (54). According to the embodiment of the transcorneal system according to the invention, the reservoir and the microspikes (53) penetrating into the skin form a structural unit. The reservoir of wall (55) and the spikes (53) are made, as described above, from a porous material whose external surface is sealed. The active ingredient solution is injected into the active ingredient matrix (52) under slight overpressure. The overpressure is maintained by elastic membrane (54) and is thus available to keep the flow rate constant. The flow rate can also be briefly increased from the outside (patient) by pressing on the membrane in order to permit an additional dose. Figure 4a shows the system according to the invention in the initial state in which the outward arched membrane (54) ensures that the active ingredient solution is under pressure and is forced into the active ingredient reservoir (52). The active ingredient goes through the transcorneal skin layer via the microspikes (53) to achieve a systemic effect.

Figure 4b shows the membrane (54) after most of the active ingredient solution is used up.

Figure 5 shows a section through a transcorneal system (1). The housing (10) contains an active ingredient reservoir (2), which is sealed on the top by a bellows (3). The active ingredient solution (4) is situated in the active ingredient reservoir and reaches a pump chamber (6) via an inlet channel (5) on the lower side of the active ingredient reservoir. The active ingredient goes via an outlet channel (7) to the microspike (8) arranged on the bottom of the housing and from there outward through the capillary openings (9) in the microspikes. The housing side parts (10a) and the housing bottom (10b) together form with the microspikes a structural unit, preferably made of thermoplastic. The cover of the housing contains the power supply in the form of a battery (11), as well as an electronic control (12), a vent (13) makes it possible for the bellows to adjust to the decreased volume upon release of the active ingredient solution to the microspikes. Supply of the active ingredient solution occurs through a piezoelectric membrane (14) which carries out an electrically driven pump movement. The inlet channel (5) is configured so that the active ingredient solution is pumped by the piezoelectric membrane (14) to the outlets of the microspikes. This occurs either through a valve or because the cross section of the inlet channel is smaller than that of the outlet channel (7). Before use of the transcorneal system, the microspikes are protected by a spike protector (15), for example, in the form of a cap.

Figure 6 shows some embodiments of the microspikes according to the invention in a section and top view.

Figure 6a shows a microspike with a central opening (9) and a cylindrical outer shape (8) and a conical tip (10).

Figure 6b shows a microspike with an opening in the form of a slit (9) and the cylindrical outer shape (8).

Figure 6c shows a microspike with a flattened outside (8) in which the opening is arranged in the form of a slit.

Figure 6d shows a microspike with cylindrical outer shape and oblique tip (10).

Figure 6e shows an embodiment of the microbezels according to the invention which can be used instead of the microspikes, in a section and top view.

The openings (9) for the active ingredient solution are ordinarily situated right next to bezel (8a) on the bottom (10b) of the reservoir (see Figure 5) so that the active ingredient solution goes from there through the scarified skin surface and can exert a systemic effect.

Figure 6f shows a embodiment of a microbezel in the form of a spike with tips, the edges (8b) that scarify the skin. The openings (9) are situated in the region of the spike.

The dimensions of the microbezels are roughly of the same order as the already described microspikes.

The individual microspikes or microbezels are typically arranged on the bottom of the transcorneal system and form a structural unit; their number is between 10 and 100, for example.

Dosage of the drug can be controlled via the volume flow, which is dependent on the sum of the cross sections of the openings of the microspikes.

Claims

1. Transcorneal system for controlled release of drugs, containing an active ingredient reservoir, as well as a device with microspikes or microbezels for administration of the active ingredient.

2. Transcorneal system according to Claim 1, characterized in that the microspikes and microbezels have a length (depth) that corresponds at least to the thickness of the corneal skin layers.

3. Transcorneal system for controlled release of drugs containing an active ingredient reservoir as well as a device with microspikes through which the active ingredient is administered in the form of a solution.

4. Transcorneal system according to Claim 1, 2 or 3, characterized in that it contains a number of microspikes on the side facing the skin.

5. Transcorneal system according to one of the preceding claims, characterized in that it contains a device that makes it possible to supply the active ingredient from the reservoir into the skin through the openings of the microspikes.

6. Transcorneal system according to one of the preceding claims, characterized in that it contains a device for power supply of the system.

7. Transcorneal system according to one of the preceding claims, characterized in that it contains devices to control and regulate active ingredient release.

8. Transcorneal system according to one of the preceding claims, characterized in that at least one limiting surface of the reservoir is designed to move.

9. Microspike for application of drug solutions, characterized in that it has a length of at least 10 µm.

10. Microspike according to one of Claims 1-8, characterized in that it has at least one capillary opening in the form of a hole and/or slit.

11. Microspikes according to Claim 9 or 10, characterized in that they are an integral component of the active ingredient reservoir.

12. Microspike according to one of Claims 9-11, characterized in that it consists of a thermoplastic.

13. Microspike according to one of Claims 9-12, characterized in that it has a tip with a radius of curvature of less than 10 µm.

14. Microspike according to one of Claims 9-13, characterized in that it consists of a porous, liquid permeable material.

15. Use of a transcorneal system, as defined in Claims 1-8, for controlled release of systemically acting drugs.

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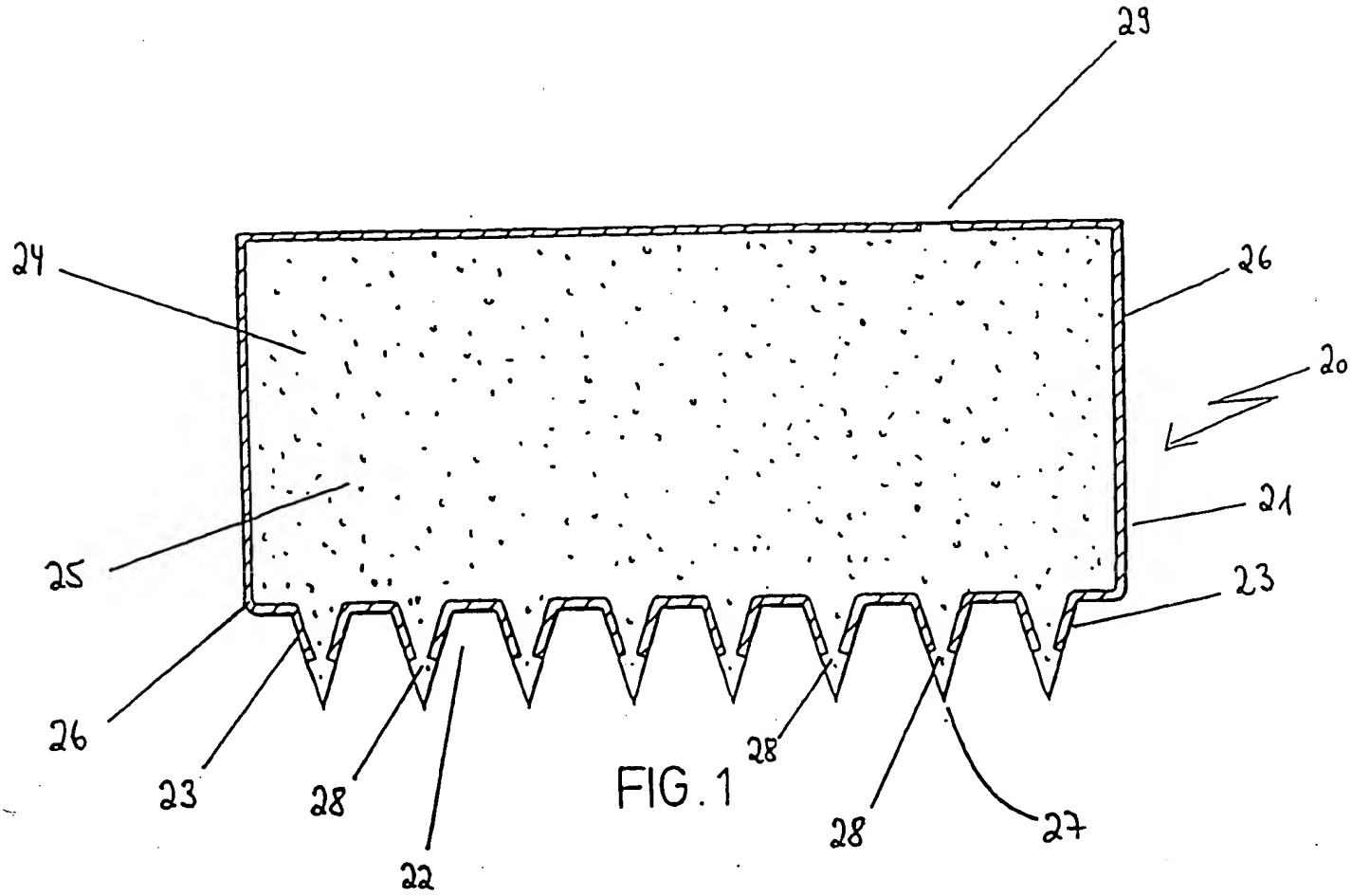

FIG. 1

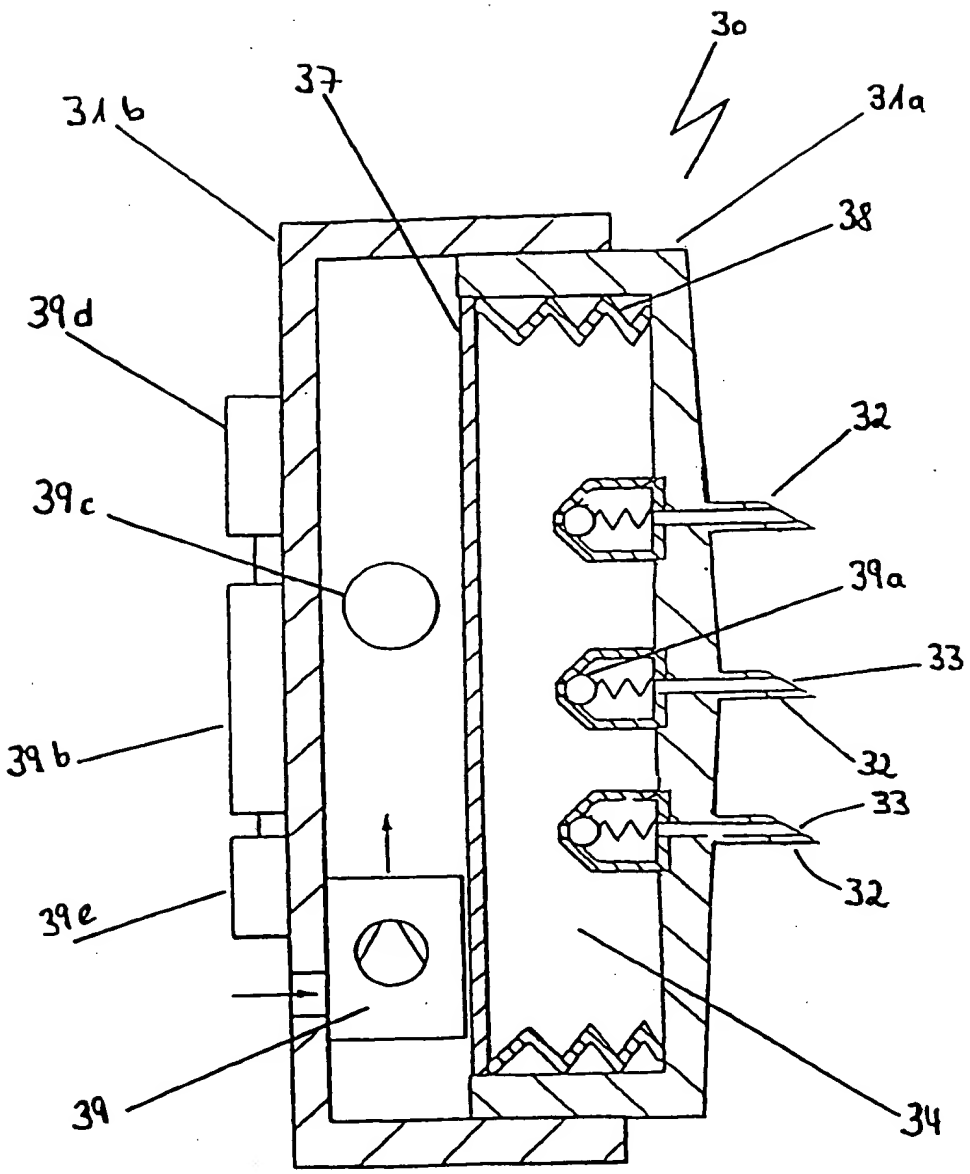

FIG. 2

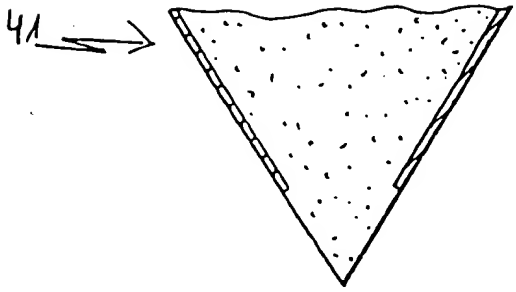

FIG. 3a

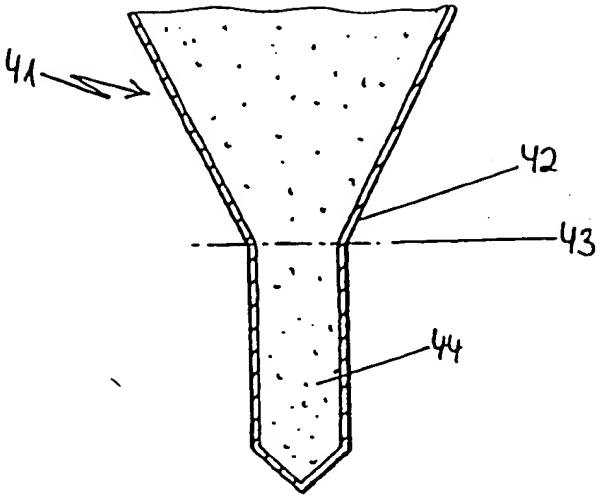

FIG. 3b

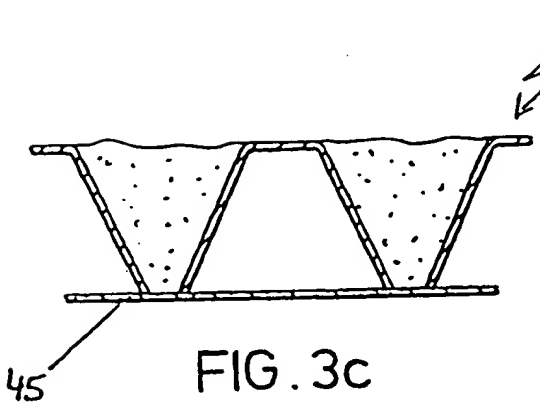

FIG. 3c

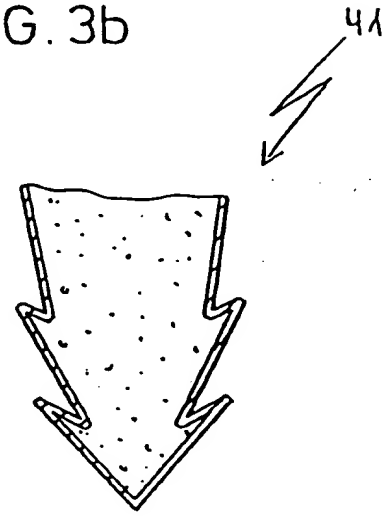

FIG. 3d

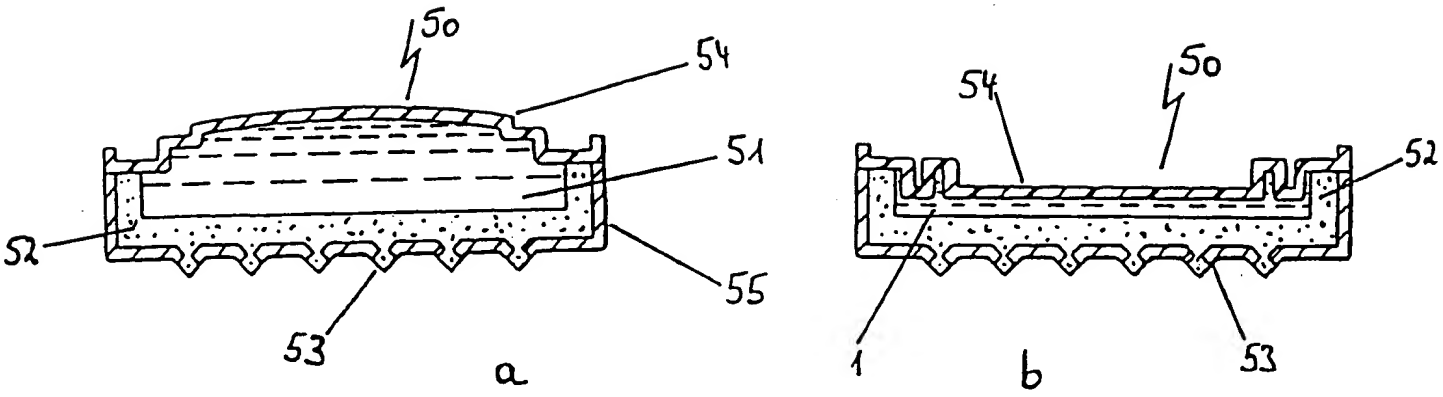
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FIG. 4

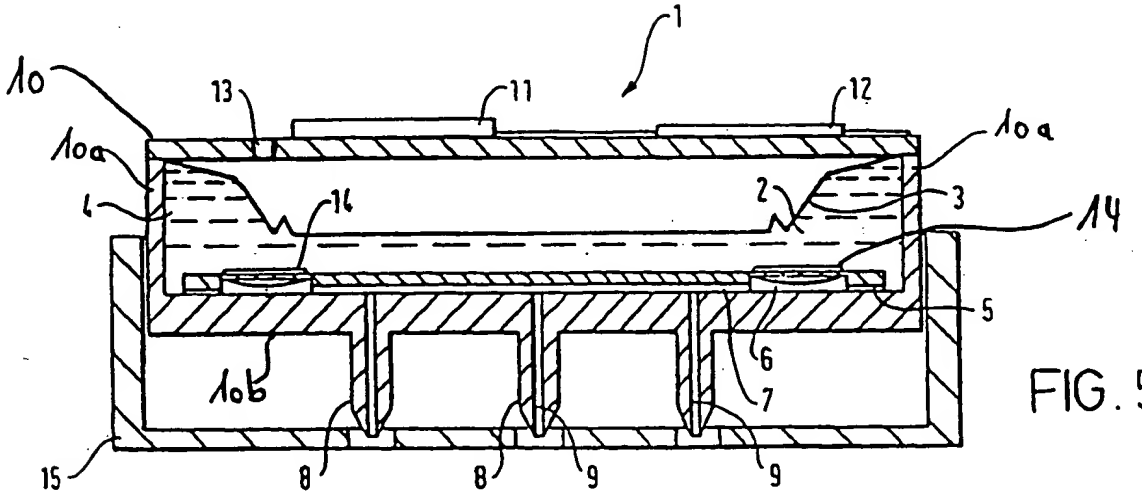
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FIG. 5

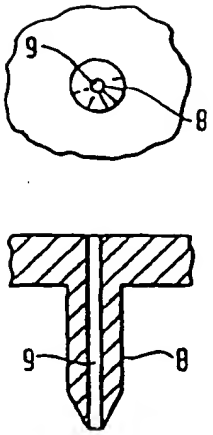

FIG. 6a

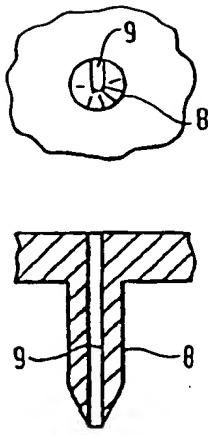

FIG. 6b

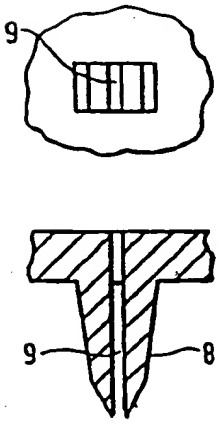

FIG. 6c

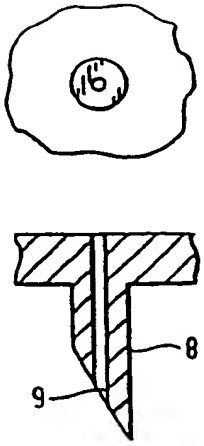

FIG. 6d

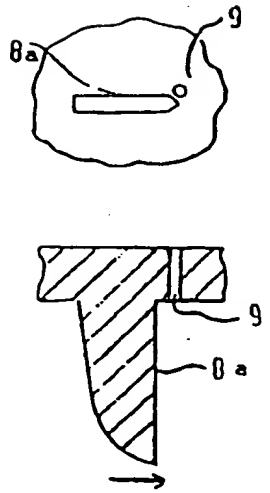

FIG. 6 e

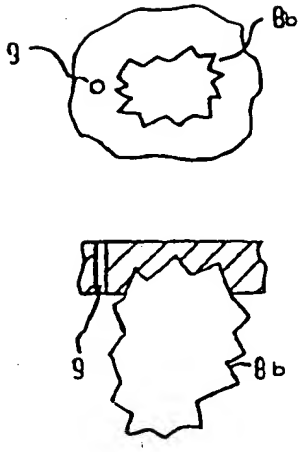

FIG. 6 f

INTERNATIONAL SEARCH REPORT

Internat : Application No
PCT/EP 96/03090

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61M37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 964 482 A (GERSTEL) 22 June 1976 see the whole document	1-5,7-15
X	GB 2 221 394 A (EILERTSEN) 7 February 1990 see page 3, line 9 - page 4, line 24; figures	1,3-5,8, 15
A	EP 0 513 879 A (DRUG DELIVERY SYSTEMS) 19 November 1992 see abstract; figures	1,3,6
P,X	DE 195 18 974 A (SAMSUNG) 30 November 1995 see abstract; figures	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 November 1996	19/11/96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Kousouretas, I

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 96/03090

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